COMPARATIVE EVALUATION OF BOLUS ADMINISTRATION OF ESMOLOL AND FENTANYL FOR PRESSOR RESPONSE ATTENUATION DURING LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

A STUDY OF 75 CASES

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BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"COMPARATIVE EVALUATION OF BOLUS ADMINISTRATION OF ESMOLOL AND FENTANYL FOR PRESSOR RESPONSE ATTENUATION DURING LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION "** is bonafide record work done by **Dr. K. VIJAYAKUMAR** under my direct supervision and guidance, submitted to The Tamil Nadu Dr. M.G.R. Medical University in partial fulfillment of University regulation for M.D, Branch X–Anaesthesiology.

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DECLARATION

I **Dr.K.VIJAYAKUMAR** solemnly declare that this dissertation titled **"COMPARATIVE EVALUATION OF BOLUS ADMINISTRATION OF ESMOLOL AND FENTANYL FOR PRESSOR RESPONSE ATTENUATION DURING LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION"** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other, for any award, degree, diploma to any other University board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of M.D., degree Branch – X (Anaesthesiology) to be held in March 2008.

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CONTENTS

INTRODUCTION

The hemodynamic responses to laryngoscopy and endotracheal intubation have been recognized since 1951. Though these pressor responses have been observed frequently they have been interpreted differently by many authors. The induction of anaesthesia, laryngoscopy, endotracheal intubation and surgical stimulation often evoke cardiovascular responses characterized by alterations in systemic blood pressure, heart rate and cardiac rhythm. The response following laryngoscopy and intubation peaks at 1-2 min and returns to baseline within 5-10 mins.

These sympathoadrenergic responses are probably of little clinical consequence in healthy patients. Complications like left ventricular failure, myocardial ischemia and cerebral haemorrhage have been attributed to sudden rise in systemic arterial blood pressure and increase in heart rate. These complications are more likely to occur in patients with pre existing hypertension, coronary heart disease, cerebral vascular disease, intracranial pathology and hyperactive airways. In such cases, reflex circulatory responses such as increase in heart rate, systemic arterial blood pressure and disturbances in cardiac rhythm need to be suppressed.

Prof. Ward and King (1960) in their combined study documented myocardial ischemic changes due to reflex sympathoadrenal response

immediately following laryngoscopy and endotracheal intubation with a mean increase in systemic pressure of 40mmHg even in normotensive patients.

Prys Roberts et al (1971) showed an exaggerated form of this response in hypertensives. Anti hypertensives modify the response but do not inhibit it completely.

The hemodynamic responses during laryngocopy and endotracheal intubation should be abolished to balance the myocardial oxygen supply and demand which is a key note in the safe conduct of Anaesthesia.

Attempts to reduce these untoward cardiovascular responses during laryngoscopy and endotracheal intubation lead to the trial of various systemic as well as topical agents.

The present concept of a definitive sympathetic overactivity during laryngeal intubation clearly shows that a more protection against vagal overactivity and the use of anticholinergic drugs alone maynot be sufficient. Those techniques which require prior laryngoscopy to administer the local anaesthetic solution are likely to be of limited value. The common strategies adapted are narcotics, vasodilators, Beta blockers, calcium channel blockers, lidocaine and other sympatholytics.

The inclusion of a rapid onset, short duration, water soluble, cardio selective β blocker, Esmolol to the armamentarium of the anaesthesiologist to

control periods of intense sympathetic stimulation, namely laryngoscopy and endotracheal intubation adds on to the safety of anaesthesia.

Fentanyl, a potent narcotic can also attenuate pressor response by maintaining proper depth of anaesthesia. Analgesic effect of fentanyl suppresses the nociceptive stimulation caused by the intubation procedure. The centrally mediated decrease in sympathetic tone observed by Lambie et al (1974), might partly be involved in pressor response attenuation.

In our study, we have compared the efficacy of bolus administration of IV esmolol and IV fentanyl to suppress the pressor response during laryngoscopy and endotracheal intubation. This study was undertaken in the Department of Anaesthesiology, Government Rajaji Hospital, Madurai Medical College, Madurai.

AIM OF THE STUDY

This study was done to compare the efficacy of bolus administration of **IV esmolol 2mg/kg** and **IV fentanyl 3 mcg/kg** in attenuating the cardiovascular stress responses accompanying laryngoscopy and endotracheal intubation by measuring heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure with control group.

NERVE SUPPLY OF LARYNX

The nerve supply of the larynx is from Vagus via superior and Recurrent laryngeal nerve branches. Superior laryngeal nerve passes deep to both internal and external carotid arteries and there divides into a small external branch which supplies cricothyroid muscle and a large internal branch which supplies the interior of larynx as far down as the vocal cords after piercing the thyrohyoid membrane.

The Recurrent laryngeal nerve on the right side leaves the Vagus as the latter crosses right subclavian artery, it then loops under the artery and ascends to the larynx in the groove between oesophagus and trachea. On the left side the same originates from the vagus as it crosses the aortic arch, then it passes under the arch to reach the groove between oesophagus and trachea. Once it reaches the neck the left nerve has the same relationship as on the right side. The recurrent laryngeal nerve provides the motor supply to the intrinsic muscles of the larynx except the cricothyroid. It also has a sensory branch which supplies laryngeal mucosa inferior to the vocal cords.

NERVE SUPPLY OF TRACHEA

The muscle fibres of the trachea, including the trachealis muscle, are innervated by the recurrent laryngeal nerves which also carry sensory fibres from the mucous membrane. Sympathetic nerve fibres are derived mainly from

the middle cervical ganglion and have connections with the recurrent laryngeal nerves.

PHYSIOLOGIC AND PATHOPHYSIOLOGIC RESPONSES TO DIRECT LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

Intubation of trachea alters respiratory and cardiovascular physiology both via, reflex responses and by the physical presence of endotracheal tube. Although the reflex responses are generally of shorter duration and of little consequences in the majority of patients, they may produce profound disturbance in patients with underlying abnormalities such as hypertension, coronary artery disease, reactive airways and intracranial neuro pathology.

Cardiovascular Responses :

The cardiovascular responses to laryngoscopy and intubation are bradycardia, tachycardia and hypertension. They are mediated by both the sympathetic and parasympathetic nervous system. Bradycardia is often seen in infants and small children during laryngoscopy and intubation. Although only rarely seen in adults, this reflex is mediated by an increase in vagal tone at the sinoatrial node and is virtually a monosynaptic response to a noxious stimulus in the airway.

The more common response to endotracheal intubation is hypertension and tachycardia mediated by sympathetic efferents via the Cardioaccelerator

nerves and sympathetic chain ganglia. The polysynaptic nature of the pathways from the vagal and Glossopharyngeal afferents to the sympathetic nervous system via the brain stem and spinal cord results in a diffuse autonomic response which includes widespread release of nor-epinephrine from adrenergic nerve terminals and secretion of epinephrine from the adrenal medulla. Some of the hypertensive response to endotracheal intubation also results from activation of the renin angiotensin system, with the release of renin from the renal juxtaglomerular apparatus, an end organ innervated by beta adrenergic nerve terminals.

Central Nervous System :

In addition to activation of the autonomic nervous system endo tracheal intubation also stimulates CNS activity as evidenced by increasing electroencephalographic activity, cerebral metabolic oxygen requirement and cerebral blood flow.

Respiratory system :

The effect of endotracheal intubation on the pulmonary vasculature is probably less well understood than the responses elicited in the systemic circulation.

AIRWAY-EFFECTS OF ENDOTRACHEAL INTUBATION

1. Upper Airway Reflex : Laryngospasm

Afferent pathyway for laryngospasm and cardiovascular responses to endotracheal intubation are mediated by the Glossopharyngeal nerve when stimuli occur superior to the anterior surface of the epiglottis and by the vagus N when stimuli occur from the level of posterior epiglottis down into the lower airway.

Laryngospasm is a monosynaptic reflex primarily elicited under light general anesthesia when vagally innervated nerve endings in the upper airway are stimulated and conscious respiratory efforts cannot override the reflex.

2. Dead Space :

Normal extrathoracic anatomical dead space of 75 ml which on intubation is reduced by 60 ml.

3. Upper Airway Resistance :

Endotracheal tube causes a mechanical burden for a spontaneously breathing patient in the form of a fixed upper airway resistance because it decreases airway caliber and increases resistance to breathing.

4. Lower Airway Resistance :

Bronchospasm can occur. Reflex increase in airway resistance may occur. Receptors in the larynx and upper trachea may cause large airway

constriction distal to the tube which in turn may extend to the smaller peripheral airways. Rapid changes in airway caliber following airway instrumentation are thought to result largely from parasympathetic activation of airway smooth muscle. Cholinergically induced broncho constriction is a normal airway response to intubation in anaesthetized patients.

5. Endotracheal tube Resistance and Exhalation :

Endotracheal tube may limit expiratory flow so that full exhalation does not occur.

6. Functional residual capacity (FRC) :

Presence of endotracheal tube tends to reduce the FRC

7. Cough :

Efficiency is reduced whenever an endotracheal tube is in place.

8. When the upper airway is bypassed following intubation the gases must be warmed and humidified.

Intubation and Cardiovascular Diseases :

The most common adverse cardiovascular problem related to intubation is myocardial ischemia in patients with coronary insufficiency. Because two of the major determinants of O2 consumption namely heart rate and blood pressure are markedly increased during intubation.

The integrity of cerebral and aortic aneurysms is largely a function of transmural pressure. Accordingly a sudden increase in blood pressure can lead to rupture of the vessels and sudden deterioration of the patients condition.

Intubation in neuropathologic disorders can cause dangerous increase in intracranial pressure and transient impairment of cerebral perfusion.

Before the advent of neuromuscular blocking drugs, intubation was only performed under such deep levels of anaesthesia that there was relatively little cardiovascular responses generated.

METHODS TO ATTENUATE CIRCULATORY RESPONSES DURING LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

The sympathoadrenal responses should be abolished as maintenance of delicate balance between myocardial oxygen supply and demand forms the keynote in the safe conduct of anaesthesia.

Various methods tried by various workers are

I. Deepening of General Anaesthesia :

Inhalational anaesthetic agents – The dose of volatile agent required to block the cardiovascular response to endotracheal intubation. This deep level of anaesthesia achieved by inhalational agents results in profound cardiovascular depression prior to endotracheal intubation. Various agents used are Halothane, Isoflurane and Seroflurane.

II Lignocaine :

a) Lignocaine gargle for Oropharyngeal anaesthesia

b) Aerosol for intratracheal anaesthesia

c) Topical spray for vocal cords

d) Regional nerve blocks – superior laryngeal nerve, glossopharyngeal nerve

e) Intravenous administration.

Topical anaesthesia of upper airway has proved to be less effective than systemic administration of lignocaine.

Mechanism :

1. By increasing the depth of general anaesthesia
2. Potentiation of effects of nitrous oxide anaesthesia and reduction of MAC for halothane by 10-28%
3. Direct myocardial depression
4. Peripheral vasodilatation
5. Anti arrhythmic properties
6. Suppression of cough reflex

III Vasodilators :

Hydralazine

Sodium Nitroprusside

Nitroglycerin

IV Narcotics :

Fentanyl

Alfentanil

Sufentanil

Morphine

Pethidine

Fentanyl is most commonly used narcotic agent. It is a

a) Potent analgesic

b) Has short duration of action

c) Doesnot increase intracranial tension during controlled ventilation

d) Minimal circulatory changes

Mechanism :

1. Analgesic effect of Fentanyl suppresses the nociceptive stimulation caused by the intubation procedure.
2. The centrally mediated decrease in sympathetic tone observed by Lambie et al, (1974) when investigating the mechanism of hypotension induced by fentanyl in dogs, might partly be involved.
3. Activation of vagal tone by fentanyl was also observed.

V – Adrenergic Blockers :

Long acting : Metoprolol, phentolamine,
Propranolol, labetalol

Short acting : Esmolol

Of these, Esmolol is most commonly used agent because of its ultra short action.

It reduces resting heart rate, systolic blood pressure, Ejection fraction and cardiac index but it maintains coronary perfusion pressure.

VI Calcium channel blockers

Nifedipine,

Nicardipine

Diltiazem

Verapamil

Nicardipine has got superior action

VII Alpha 2 agonist

Clonidine – suppresses the increase in sympathetic activity evoked by the intubation.

VIII – Midazolam :

Sedation and anxiolytic

IX - Magnesium Sulphate :

Sedation and anxiolytic

PHYSIOLOGY OF BETA – RECEPTORS

Autonomic nervous system regulate body's ongoing physiological function automatically by a dual function.

First by maintaining an internal environment, and secondly by preparing and enabling the body to undertake extra efforts in situations of threat to the body's well being.

Parasympathetic cholinergic system is a restorative system. Sympathetic adrenergic is primarily stimulatory preparing the body for fight or flight.

In cardiovascular system sympathetic and parasympathetic system are in constant opposition, and the state of the system depends on which system predominates.

AHLQUIST (1960) characterized sympathetic stimulation as being predominantly mediated through alpha or beta receptor effects. Lands et al (1961) observed that beta receptor activity is due to two forms, beta 1 and beta 2 receptor stimulation and is responsible for the effect of sympathetic nervous activation on the heart, smooth muscle relaxation in vascular and respiratory systems, renin release, tissue lipolysis and glycogenolysis.

Beta 1 receptor is primarily involved in cardiac effects. In special circumstances like chronic cardiac failure beta 2 receptors may also mediate cardiac activity.

In congestive cardiac failure beta 1 density decreases without changes in beta 2 receptor accounting for higher inotropic response by isoproterenol.

Beta agonist posses higher affinity for coupled activator forms of the receptor, whereas beta antagonists have affinity for both active and inactive forms with no cellular activity. In addition antagonists maintain the receptors in a relatively inactive form so that considerably more agonists are required to unbalance the equilibrium.

BETA RECEPTOR ANTAGONISTS

Most of the currently available β–blocking drugs are propranolamines. The commercial formulation is a racemic mixture, in which the "L" form is the active ingredient.

INDICATIONS

They are of use in

a) Cardiac arrhythmias which are principally due to sympathetic stimulation as in phaeochromocytoma, myocardial infarction and arrhythmias associated with anaesthesia.

b) Ischemic heart disease – improves Oxygen supply – demand ratio.

c) Hypertensive cardiovascular disease – associated with a high plasma renin activity.

d) Thyrotoxicosis

e) Obstructive cardiomyopathy

f) Phaeochromocytoma, Hereditory Tremors, Anxiety neurosis, Schizophrenia, Drug addiction and Migraine

Adverse Reactions :

a. Bronchoconstriction

b. Cardiac Failure

c. Peripheral vascular insufficiency

d. Hypoglycemia and

e. Drug interaction (e.g.,) antidiabetics.

THE BETA ADRENERGIC BLOCKING DRUGS

Drugs	Potency propranolol=1	Beta selective	Intrinsic sympatho mimetic	Membrane Stabilizing activity	Lipid solubility	Hepatic metabolism
Propranolol	1	-	-	+	High	99
Timolol	6	-	-	-	Moderate	80
Nadolol	0.8	-	-	-	Low	27
Metoprolol	1	++	-	-	Moderate	97
Atenolol	1	++	-	-	Low	< 10
Pindolol	6	-	+++	+	Mod/Low	60
Oxprenolol	1	-	++	+	Moderate	97
Acebutolol	0.3	+	+	+	High	80
Labetalol	0.3	-	-	-	Mod/High	90+
Esmolol	0.5	+++	-	-	Low	0-10

PHARMACOLOGY OF ESMOLOL

In 1982, ZAROSLINSKI described the concept of an ultrashort acting β -adrenergic blocker. From this work esmolol which is a cardioselective β-blocker that has an extremely short duration of action was subsequently identified and characterized.

Chemistry :

Esmolol is chemically Methyl p- [2-hydroxy -3 (isopropylamino) propoxy] hydrocinnamate hydrochloride, a molecular structure characteristic of second generation β -blockers. Esmolol contains an ester in the para position of phenyl ring. The presence and location of this ester is of fundamental importance in the determination of Esmolol's cardioselectivity as well as its ultrashort action.

Esmolol has the empirical formula C_{16} H_{26} NO_4 C_1 and a molecular weight of 331.8. It has one asymmetric centre and exists as an enantiomeric pair.

Esmolol hydrochloride is a white to off-white crystalline powder. It is a relatively hydrophilic compound which is very soluble in water and freely soluble in alcohol.

Clinical Pharmacology :

Esmolol hydrochloride is a β_1–selective (cardioselective) aderenergic receptor blocking agent with rapid onset, a very short duration of action and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dose. It inhibits the β_1 receptors located chiefly in cardiac muscle, but their preferential effect is not absolute and at higher doses it begin to inhibit β_2- receptors located chiefly in the bronchial and vascular musculature. Esmolol is 43 fold more potent at β receptors in atria (β_1) than in Trachea (β_2). Blockade of vascular β–receptors required a dose several – fold greater than that required for cardiac β–blockade. Esmolol does not have any effect on peripheral vascular resistance.

Pharmacokinetics and Metabolism :

Esmolol is rapidly metabolished by hydrolysis of ester linkage, chiefly by esterase in the cytosol of red blood cells and not by plasma cholinesterase or red cell membrane acetylcholinesterase. Total body clearance in man was found to be 20 L / kg / hr which is greater than cardiac output. Thus the metabolism of Esmolol is not limited by the rate of blood flow to the metabolising tissues such as the liver and kidney. It has a rapid distribution half-life of about 2 minutes and an elimination half-life of about 9 minutes.

After an appropriate loading dose, steady state blood levels of Esmolol are obtained within 5 minutes. Steady state is obtained within 30 minutes, without a loading dose. Steady state blood levels are maintained during infusion but fall rapidly after termination of the infusion (20 minutes). Since it has a short half-life, blood levels can be rapidly altered by increasing or decreasing the infusion rate.

Metabolism of Esmolol results in the formation of an acid metabolite (ASL-8123) phenyl propionic acid and methanol. The acid metabolite has $1/1500^{th}$ the activity of Esmolol and its blood levels do not correspond to the level of β – blockade. Acid metabolite has an elimination half life of about 3.7 hrs and is excreted in the urine with a clearance approximately equal to the glomerular filtration rate. Elimination of acid metabolite is significantly decreased in patients with renal disease with the elimination half-life increased to ten-fold that of normal. Esmolol is unaffected by plasma cholinesterase. For full enzymatic activity, the Esmolol esterase in RBC cytosol requires a heat – labile high molecular weight plasma component. The enzyme is not inhibited to any significant degree of cholinesterase inhibitor such as physostigmine or echothiophate, but is totally inhibited by sodium fluoride. No metabolic interactions has been observed between Esmolol and other ester containing molecules of clinical relevance. It does not modify the magnitude or duration of

neuromuscular blockade in response to succinylcholine (Richard J.Gorzynski). Esmolol is 55% bound to human plasma protein while acid metabolite is only 10% bound.

In human electrophysiological studies Esmolol produced effects typical of a β – blocker ; decrease in heart rate, increase in sinus cycle length, prolongation of sinus node recovery time.

1. Esmolol produces reduction in heart rate, systolic blood pressure, rate pressure product and right ventricular ejection fraction and cardiac index at rest and during exercise, similar in magnitude to propranolol, but produces significantly lower fall in systolic blood pressure ; Esmolol also produces small, clinically insignificant increase in left ventricular end-diastolic pressure and pulmonary capillary wedge pressure. 30 minutes after discontinuation of infusion all the haemodynamic parameters return to pretreatment levels.

2. Cardioselectivity of Esmolol was demonstrated by infusion of Esmolol in asthmatic patients which produced no significant increase in specific airway resistance compared to placebo. Unlike Esmolol, propranolol produces significant bronchospasm requiring bronchodilator therapy. Esmolol shows no adverse pulmonary effects in patients with COPD.

3. Esmolol is very effective in the management of supraventricular tachycardia, atrial fibrillation and atrial flutter.

There is significant decrease in blood pressure compared to propranolol but was rapidly reversible with decreased infusion rates or on discontinuation. Hypotension was less frequent in those patients receiving concomitant digoxin.

Drug Interactions :

Catecholamine depleting drugs (eg. Reserpine) may have an additive effect when given with Esmolol. So patients should be observed for hypotension or marked bradycardia.

Esmolol concentrations were higher when given with warfarin but this is of no clinical importance. When given with digoxin blood levels of digoxin were high and when given with morphine blood levels of Esmolol were high.

Indications :

For rapid control of ventricular rate as in atrial flutter or fibrillation. For short term control of ventricular rate when short acting agents are desirable as in (SVT, unstable angina, myocardial infarction) and to control perioperative tachycardia.

Contraindications :

In patients with sinus bradycardia, heart block, cardiogenic shock and overt cardiac failure, diabetics and end stage renal disease.

Adverse Reactions :

CVS – Symptomatic hypotension occurs in 12% of patients. Asymptomatic hypotension in 25% of patients. Hypotension gets resolved on discontinuation of treatment. Very rarely bradycardia, chest pain, syncope, sinus pause and asystole occur all reversible with discontinuation of treatment.

CNS : Dizziness, Headache, agitation and fatigue.

RS : Bronchospasm, nasal congestion – relatively less.

GIT : Nausea, vomiting, constipation, Diarrhoea, Drymouth.

Skin :

Inflammation, and induration at the site of infusion, Oedema, skin discolouration, thrombophlebitis and local skin necrosis.

Acute Toxicity :

Accidental massive overdose when it occurs is due to an error in dilution. It can cause hypotension, bronchospasm, drowsiness, bradycardia and loss of consciousness. These are resolved within ten minutes of discontinuation or with administration of a pressor agent.

Compatibility :

Compatible with commonly used intravenous fluids except sodium bicarbonate injection.

Preparations Available :

100 mg - 10 ml vial

2.5 g - 10 ml amp

Dosage :

To attenuate the sympathoadrenal response during laryngoscopy and intubation, the dosage is 1.5 mg/kg as bolus or as an infusion at the rate of 500 mcg/kg/minute for 2 minute as loading dose followed by a maintenance dose of 100 mcg/kg/minute.

To initiate treatment of a patient with supraventricular tachycardia, a loading dose of 500 mcg/kg/minute for 1 minute followed by maintenance infusion of 50 mcg/kg/minute for 4 minutes. If an adequate therapeutic effect is not observed within 5 minutes, the same loading dose can be repeated and followed with a maintenance infusion increased to 100 mcg/kg/min, therapeutic plasma level being 400-1200 nano gm/ml. The time to 100% recovery is 30 minutes.

PHARMACOLOGY OF FENTANYL

Fentanyl is a synthetic narcotic agonist that is related to the phenyl piperidines. Acts at μ receptors as an agonist. Fentanyl when compared to morphine-a prototype opioid as an analgesic is 80-100 times more potent, has a more rapid onset and shorter duration of action than morphine.

Structure :

Fentanyl is chemically identified as N -1(1-phenethyl – 4 piperidyl propionanilide citrate).

The empirical formula is C_{22} H_{28} N_2O C_6 H_8 O_7.

Availability :

Ampoules – 2 ml containing 100 micrograms (Fendrop, Fenstrong)

10 ml ampoules containing 50 μg per ml.

Lollipop – for paediatric use

Patches – Transdermally delivering 75-100 μg/hr

Routes of Administration :

Fentanyl is the only opioid available for various forms of administration.

- Intramuscular
- Intravenous
- Neuraxial – Spinal, Epidural administration for intra and post operative analgesia.

- Transdermal – applied before the induction of anaesthesia and left in place for 24 hours. Reduces the amount of parental opioid requirement or post operative analgesia.
- Transmucosal – To decrease anxiety and to facilitate induction of anaesthesia especially in children.

Pharmacodynamics :

Acute effects :

CNS

Analgesia	Cough suppressant
Sedation	Miosis
Hypnosis	Nausea, vomiting
Euphoria	Skeletal muscle rigidity
Respiratory depressant	

CVS	**Others**
Vasodilatation	Smooth muscle spasm
Bradycardia	Histamine release
Hypotension	Decreases the stress response

Chronic effects :

Tolerance

Physical dependance

Mechanism of Action :

I – CNS effects :

1. Analgesia and Mood effects :

a. The processing of pain information is inhibited by a direct spinal effect of dorsal horn.

b. Rostral transmission of pain signals is decreased by activation of descending inhibitory pathways in the brainstem.

c. Emotional response to pain is altered by opioid actions in the limbic cortex.

d. Act at receptors located peripherally on sensory neuron.

2. Respiratory Depression :

Direct effect on respiratory centre in the medulla.

3. Antitussive – Direct effect on cough centre in medulla

4. Miosis – Stimulation of Edinger – Westphal nucleus of IIIrd nerve.

5.Nausea, vomiting : Stimulation of chemoreceptor trigger zone complex, interaction of dopaminergic, cholinergic or serotonergic mechanism.

6. Muscle rigidity : By acting at the receptor in the striatum, increases the rate of striatal dopaminergic biosynthesis and inhibits the release of the inhibitory neurotransmitter GABA.

II - Cardiovascular System :

a) Bradycardia : Stimulation of central vagal nucleus

b) Peripheral vasodilatation : Depression of vasomotor centre in medulla

c) Decreased central sympathetic tone : Raising the arrhythmogenic threshold

d) Hypotension : Especially in patients with elevated sympathetic tone like hypovolemia, cardiac failure.

III – Neuro endocrine effects :

Fentanyl and its congener are more effective in modifying hormone responses to surgery.

Analgesic effect of fentanyl suppresses the nociceptive stimulation caused by intubation procedure.

IV - Tolerance :

Acute tolerance or tachyphylaxis,

Chronic tolerance,

Cross tolerance to other opioid agonist,

Develops most rapidly to depressant effects of opioids.

Pharmacokinetics :

Fentanyl administered IV has a more rapid onset and shorter duration of action. The greater potency and more rapid onset of action reflects the greater lipid solubility which facilitates its passage across the blood-brain barrier.

The short duration of action of a single dose of fentanyl reflects its rapid redistribution to inactive tissue sites such as fat and skeletal muscles, with an

associated decrease in the plasma concentration of the drug. The lungs also serve as a large, inactive storage site, with an estimated 75% of the initial fentanyl dose undergoing first pass pulmonary uptake.

Fentanyl is extensively metabolished by dealkylation, hydroxylation and amide hydrolysis to inactive metabolites, including norfentanyl and desproprionylnorfentanyl that are excreted in bile and urine.

The pharmacokinetics of fentanyl can be described as three compartment model with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half time of 219 minutes. The volume of distribution is 4 L / kg.

Onset time and Duration of action :

Route of administration	Onset of time (minutes)	Duration of action (hours)
IM	7 – 8	1 – 2
IV	Immediate	0.5 – 1

Clinical uses :

- As a narcotic analgesic during premedication, induction and maintenance of anaesthesia and in post operative period as need arises.
- To blunt the circulatory response to direct laryngoscopy for intubation and as an adjuvant to inhaled anaesthetics to prevent sudden changes in the level of anaesthesia due to surgical stimulation.

- As an anaesthetic agent with oxygen, in high risk patients such as those undergoing open heart surgery or certain complicated neurological or orthopaedic procedures.
- As a neuroleptic anaesthetic agent with neuroleptic agents like droperidol.
- Neuraxially either alone or in combination with local anaesthetic to improve the quality of the blockade intraoperatively or for post operative analgesia.

Dosage :

IM : 50 – 100 µg (1-2 µg/kg)

IV : Low dose of fentanyl 1-2 µg / kg - To provide analgesia

2 - 20 µg / kg IV - Administered as an adjuvant to inhaled anesthetics in an attempt to blunt circulatory responses to direct laryngoscopy for intubation of the trachea or sudden changes in the level of surgical stimulation.

50 – 150 µg / kg IV (large doses of fentanyl) To produce surgical anaesthesia

Intrathecal : 10-50 µg (0.25 – 0.5 µg / kg)

Epidural : Bolus dosing – 1 µg / kg

Continuous infusion after the bolus - 30-100 µg / hr

Oral transmucosal fentanyl : 15-20 µg / kg

Transdermal fentanyl Patch : 75-100 µg/hr

Adverse effects :

Respiratory depression	Dizziness
Rigidity	Blurred vision
Laryngospasm	Emesis
Apnoea	Diaphoresis
Hypotension	
Bradycardia	

Drug interactions :

1. Nitrous oxide potentiates cardiovascular depression when given with higher doses of fentanyl.
2. Even relatively small doses of diazepam may cause cardiovascular depression when administered with high dose of fentanyl.
3. Fentanyl and tranquilizer can lead to hypotension
4. Fentanyl and MAO inhibitors can lead to hypotension.

REVIEW OF LITERATURE

Though laryngoscopy and intubation were performed with ease in yester years, the Anaesthesiologists had to struggle to combat or subdue the circulatory or cardio vascular effects of the said procedure in patients with compromised circulatory system.

RIED&BRACE (1940) postulated that reflex circulatory responses to laryngeal instrumentation were mediated through the vagus nerve and they named it as “Vaso Vagal Reflex”.

KING et al (1951) used deep Ether anaesthesia to abolish the reflex circulatory response to tracheal intubation.

KING and his associates (1960) believed the reflex mechanisms to be essentially non-specific in character. They stated that the impulses initiating the reflex arc are probably carried over the vagus, while the effector system is less clearly defined and may be due to decreased parasympathetic or increased sympathetic adrenal activity.

WYCOFF C.C.(1960) in his study stated that topical anaesthesia of the pharynx along with Superior laryngeal nerve blocks, reduced the increase in mean arterial pressure after intubation.

FORBES and DALLY (1970) observed that laryngoscopy and endo tracheal intubation is immediately associated with an average increase in mean arterial pressure of 25mm of Hg in all 22 normotensive patients. These responses were interpreted as due to reflex sympathetic adrenal stimulation.

PRY ROBERT et al (1971) found that the increases in heart rate and blood pressure are much more exaggerated in hypertensive patients.

FOEX et al (1971) observed

i. Inotropic Failure

ii. Ischemic arrhythmias and

iii. Cerebrovascular accidents.

In patients with uncontrolled hypertension who came up for emergency surgery and associated substantial increase in heart rate and blood pressure following laryngoscopy and endotracheal intubation which lasted for several minutes.

DENLINGER J.K and ELLISON N.E. (1974) have used intratracheal lignocaine spray which causes a 50% reduction in the hypertensive response.

VICTORIA FARIA BALNC and NORMAND A.G. (1974) in their article of "Complications of Tracheal Intubation" have classified the neurogenic or reflexly mediated complication into three different categories.

i. Laryngo Vagal Reflexes- Which give rise to spasm of the glottis, bronchospasm, apnoea, bradycardia, cardiac dysrhythmias and arterial hypotension. The mere presence of the tracheal tube seems to be the most common cause of bronchospasm in anaesthetized asthmatic patients.

ii. Laryngo Sympathetic Reflexes- which include tachycardia tachyarrhythmias, acute arterial hypertension as frequent complication. The hypertensive hyperdynamic state during laryngoscopy may be related in some cases to an increased noradrenaline fraction of the total catecholamines.

iii. Laryngo Spinal Reflexes- which include coughing, vomiting and bucking

LUNN (1979), BENNETT and STANLEY (1980) have observed that induction dose of fentanyl 150 mcg/kg or even as little as 4mcg/kg given 10 min after nitrousoxide – oxygen induction abolished the increase in blood pressure and heart rate.

J.CURRAN, M.CROWLEY (1980) have studied the use of Droperidol an alpha blocker to attenuate the pressor response. Droperidol administration was found to be associated with an undesirably low mean arterial pressure for a short period in a proportion of patients.

ELLIOFF et al (1980) by echo cardiographic study found that there was substantial worsening of left ventricular wall function – akinesia, dyskinesia or hypokinesia following laryngoscopy and endotracheal intubation.

DONAL E.MARTIN (1982) have also proved the efficacy of a low dose fentanyl along with an induction dose of thiopentone, but in these series, it was also found that the incidence and occurrence of tachycardia was not prevented.

V.M.KAVTTO (1982) studied attenuation of the circulatory response to laryngoscopy and intubation - fentanyl 6mcg /kg completely abolished these responses.

T.E BLACK, B.KAY AND T.E.J SLEACY (1984) compared alfentanil with fentanyl in reducing the haemodynamic responses to laryngoscopy and intubation and found that no increase were noted in groups receiving 30 mcg/kg alfentanil or 5

mcg/kg of fentanyl and alfentanil effect appears to have a shorter duration than that of fentanyl.

B.KAY, T.E.J. HAECY and P.M. BOLDER (1985) compared fentanyl and nalbuphine in blocking the circulatory response to tracheal intubation and found that nalbuphine attenuated the mean pressure response to these maneuvers but had no effect in the accompanying tachycardia and fentanyl 5 mcg/kg prevents these responses however at the cost of significant decrease in both blood pressure and heart rate and increase in respiratory depression.

DONAL R.MILLER and RAYMOND J.MARTINEAN (1989) used bolus dose of esmolol for treating hypertension, tachycardia and myocardial ischemia intraoperatively.

PARNASS SM, ROTHENBERG DM, KERCHBERGER JP and IVANKOVICH AD (1990) demonstrated that single bolus dose of esmolol blunted tachycardia and hypertensive response to laryngoscopy and endo tracheal intubation.

STEVEN M. HELFMAN, MARTIN I GOLD, EVERTARD A, DE LESSER and CLAIRE A. HERRINGTON (1991) observed that esmolol provides consistent and reliable protection from increase in both heart rate and systolic blood pressure during and after intubation. Where as lignocaine and fentanyl failed to protect against increases in heart rate but provided protection against increase in systolic blood pressure equivalent to that provided by esmolol.

D.R.MILLER and R.J. MARTENEAN (1991) concluded that esmolol 1.5mg/kg is safe and effective in controlling cardiovascular responses during anaesthetic induction.

HELFMAN SM, GOLD MI, DELISSER EA, HERRINGTON CA in 1991 demonstrated that only esmolol provided consistent and reliable protection against increase in both heart rate and systolic blood pressure accompanying laryngoscopy and intubation.

FENQ CK, CHAN KH, LOKN, ORCH, LECTY in 1996, observed that only esmolol could reliablly offer protection against increase in both heart rate and systolic blood pressure, low dose fentanyl (3mcg/kg) prevented hypertension but not tachycardia and 2mg/kg lidocaine has no effect to blunt adverse haemodynamic response during layngoscopy and tracheal intubation.

HUSSAIN AM, SULTAN ST (1999) concluded that bolus injection of fentanyl 2mcg/kg 2 minutes prior to laryngoscopy and intubation failed to protect against elevation of both the heart rate and systolic blood pressure, whereas esmolol at 2mg/kg provided consistent and reliable protection against the increase of heart rate but not arterial blood pressure.

MATERIALS AND METHODS

75 patients of ASA physical status I undergoing elective surgical procedure under General Anaesthesia with endotracheal intubation were included in the study.

Patients belonging to age group of 18-60 years of both sexes were included.

It is a prospective randomized controlled study. The study was conducted after getting approval by our institution ethical committee and after obtaining written informed consent from the patient. The surgeon was also duly informed of the study.

The study was done during the period from January 07 to June 07 in the Department of Anaesthesia, Government Rajaji Hospital, Madurai.

Inclusion Criteria :

ASA I physical status

Patients with airway with modified mallampati Grade I & II

Exclusion Criteria :

Patients with full stomach

Patients posted for emergency surgery

Patients with difficult airway

Hypertension, diabetes mellitus, Ischemic heart disease, pregnancy

Patients with contraindication to study drug

Patients refusal

Materials :

Inj. Thiopentone 2.5%

Inj. Succinyl choline

Inj. Glycopyrrolate

Inj. Midazolam

Inj. Esmolol hydrochloride

Inj. Fentanyl

Disposable 20 ml syringe

Laryngoscopy blade 3,4

Endotracheal tube of various sizes

Multichannel monitor

Monitors :

Non invasive automated blood pressure

ECG

Pulse oximetry

Methods :

Patients of both the sexes of ASA physical status I undergoing surgical procedure were randomly allocated into 3 groups.

Group C Control 10 ml of normal saline

Group E Esmolol 2 mg / kg

Group F Fentanyl 3 mcg /kg

Preoperative preparations :

All the patients were admitted and they underwent routine investigations.

Hb %

Blood Sugar

Urea

Serum Creatinine

Electrolytes

X ray chest

ECG

Other investigations were obtained on the basis of the condition of the patient.

ANAESTHESIA PROTOCOL

Preoperative visit was done to allay anxiety and good rapport was established with the patients.

All the patients were given preoperative night sedation with tab. Diazepam 10 mg orally.

Premedication :

All patients received injection Midazolam 0.05 mg/kg and Injection glycopyrrolate 0.2 mg intramuscularly 45 minutes before surgery. Preoperative heart rate and blood pressure were recorded.

Induction :

Preoxygenation was done for 3 minutes. Base line heart rate and blood pressure were recorded.

This was followed by administration of normal saline 10ml in group C, Esmolol 2 mg/kg in Group E and Fentanyl 3 mcg/kg in Group F. 1 minute after the study drug all patients were induced with thiopentone sodium in a dose of 5 mg/kg body weight followed by succinyl choline 1.5 mg / kg body weight. Intubation was performed by the same person with the correct size cuffed endotracheal tube.

Maintenance :

Anaesthesia was maintained with controlled ventilation with nitrous oxide 66% and oxygen 33%. No surgical stimulation was permitted for 7 minutes after intubation.

Monitoring :

An assistant was assigned to check heart rate and systolic blood pressure, diastolic blood pressure by auscultation at the time of preinduction, after

induction, during laryngoscopy and intubation and thereafter for next seven minutes at an interval of 1 minute. Results were tabulated.

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2002).

Using this software, frequencies, percentage, range, mean, standard deviation, x^2 and 'p' values were calculated. A 'p' value less than 0.05 is taken to denote significant relationship.

OBSERVATION AND RESULTS

75 patients under this study were categorized into 3 groups. They comprised both sexes with age ranging from 18-60 years.

1. ***Group C (Control) :*** consisting of 25 patients who received 10 ml normal saline, 3 minutes prior to laryngoscopy.

2. ***Group E (Esmolol) :*** consisting of 25 patients who received 2 mg / kg, 3 minutes prior to laryngoscopy.

3. ***Group F (Fentanyl) :*** consisting of 25 patients who received 3 mcg/kg, 3 minutes prior to laryngoscopy.

RESULTS

Demographic profile of cases included in the study

Table 1 : Age

Age Group (in years)	Control Group	Esmolol Group	Fentanyl Group
Less than 20	-	2	4
20 – 29	5	7	8
30 – 39	11	8	7
40 – 49	7	5	4
50 & above	2	3	2
Total	25	25	25
Mean	36.2	34.5	31.5
S.D	8.2	12.0	10.8
'P' Significance	**0.1605 (Not Significant)**		

There is no significant difference in the age composition of the cases in the three groups.

Table 2 : Sex

Sex	Control Group	Esmolol Group	Fentanyl Group
Males	13 (52%)	13 (52%)	14 (56%)
Females	12 (48%)	12 (48%)	11 (44%)
Total	25 (100%)	25 (100%)	25 (100%)

The sex composition of the three groups are nearly identical.

Table 3 : Weight

Weight in kgs	**Control Group**	**Esmolol Group**	**Fentanyl Group**
Mean	53.5	54.4	55.6
S.D	4.8	6.1	7.9
'p'	**0.4186**		
Significance	**Not significant**		

The mean weight of the three groups does not difference significantly.

Heart rate, systolic and diastolic blood pressure were recorded before induction, at the time of laryngoscopy and intubation and at 1 min interval for 7 min thereafter.

Table 4 : Basal Heart Rate, Systolic Blood Pressure, Diastolic blood pressure and Mean arterial Pressure

Basal Rates	**Control Group**	**Esmolol Group**	**Fentanyl Group**	**'p'**	**Significance**
Heart Rate	81.9 ± 12.9	86.9 ± 10.8	87.4 ± 11.9	**0.0689**	**Not Significant**
Systolic B.P	123.5 ± 7.9	127.8 ± 9.5	127 ± 8.4	**0.2289**	**Not Significant**
Diastolic B.P	78.3 ± 5.7	81 ± 5.2	82.5 ± 4.9	**0.056**	**Not Significant**
Mean arterial pressure	93.6 ± 6.1	96.6 ± 6.2	97.3 ± 5.4	**0.1033**	**Not Significant**

Table shows the preoperative means heart rate, mean systolic mean diastolic blood pressure in groups C, E, F.

There is no statistical difference in the mean heart rate, mean systolic, mean diastolic blood pressure across 3 groups. (p> 0.05).

Table 5 : Heart Rate, Systolic Blood Pressure, Diastolic blood pressure and Mean arterial Pressure after induction

After induction	Control Group	Esmolol Group	Fentanyl Group	'p'	Significance
Heart Rate	92.1 ± 11.4	81 ± 9.8	88.2 ± 11.6	**0.0025**	**Significant**
Systolic B.P	123.6 ± 8.9	117.1 ± 11.2	118.4 ± 10.9	**0.0949**	**Not Significant**
Diastolic B.P	79.3 ± 5.7	76.6 ± 5.7	76.2 ± 6.0	**0.1604**	**Not Significant**
Mean arterial pressure	94 ± 6.5	90 ± 6.9	90.4 ± 6.2	**0.1311**	**Not Significant**

Table shows the mean heart rate, mean systolic and mean diastolic blood pressure after induction. There is statistically significant difference in mean heart rate of patients across 3 groups (p< 0.01). The mean heart rate of esmolol group is lower than that of both the control and fentanyl group.

There is no statistical difference in the mean systolic and diastolic blood pressure among 3 groups.

Table 6 : Heart Rate, Systolic Blood Pressure, Diastolic blood pressure and Mean arterial Pressure at laryngoscopy and endotracheal intubation

At intubation	Control Group	Esmolol Group	Fentanyl Group	'p'	Significance
Heart Rate	108.6 ± 11.7	91 ± 10.6	102.7 ± 11.9	**0.0001**	**Significant**
Systolic B.P	152.1 ± 8.6	139.6 ± 7.2	142.8 ± 12.1	**0.0001**	**Significant**
Diastolic B.P	95.2 ± 6.5	88.6 ± 6.0	94.6 ± 11.1	**0.0013**	**Significant**
Mean arterial pressure	113.5 ± 6.5	105. 7 ± 5.5	110.6 ± 10.7	**0.0004**	**Significant**

Table shows the mean heart rate, mean systolic and diastolic blood pressure at laryngscopy and endotracheal intubation.

There is high statistically significant difference in mean heart rate across the 3 groups ($p < 0.001$). The mean heart rate, blood pressure and mean arterial pressure of the esmolol group are the least. The difference with the control group and fentanyl group are statistically significant.

Table 7 : Heart Rate, Systolic Blood Pressure, Diastolic blood pressure and Mean arterial Pressure at 1 minute

At 1 minute	Control Group	Esmolol Group	Fentanyl Group	'p'	Significance
Heart Rate	110.6 ± 11.6	92.4 ± 10.8	103.5 ± 12.5	**0.0001**	**Significant**
Systolic B.P	157.2 ± 6.9	139.2 ± 9.2	142.9 ± 12.1	**0.0001**	**Significant**
Diastolic B.P	99.1 ± 6.0	88.7 ± 5.9	94.6 ± 10.5	**0.0001**	**Significant**
Mean arterial pressure	118.6 ± 5.4	105.6 ± 5.9	110.6 ± 10.3	**0.0001**	**Significant**

Table shows the mean heart rate, mean systolic and diastolic blood pressure at 1 minute following intubation.

There is statistically significant difference in mean heart rate of patients across 3 groups ($p < 0.001$). The heart rate are lowest in esmolol group followed by fentanyl group and then control group.

Mean systolic and diastolic pressure are having statistically significant among 3 groups ($p < 0.01$). The blood pressure and mean arterial pressure are lowest in the esmolol group followed by fentanyl and control group.

Table 8 : Heart Rate, Systolic Blood Pressure, Diastolic blood pressure and Mean arterial Pressure at 2 minutes

At 2 minutes	Control Group	Esmolol Group	Fentanyl Group	'p'	Significance
Heart Rate	105.2 ± 11.3	90.3 ± 8.4	100.3 ± 10.3	**0.0001**	**Significant**
Systolic B.P	150 ± 8.5	133.5 ± 7.5	139.5 ± 11.2	**0.0001**	**Significant**
Diastolic B.P	95.5 ± 6.6	84 ± 5.1	90.8 ± 11.2	**0.0001**	**Significant**
Mean arterial pressure	113.2 ± 6.3	100.5 ± 4.9	106.8 ± 10.0	**0.0001**	**Significant**

Table shows the mean heart rate, mean systolic and diastolic blood pressure at 2 minutes following intubation.

There is high statistically significant difference in mean heart rate, blood pressure and mean arterial pressure of patients across 3 groups ($p < 0.001$).

Patients is esmolol group are having significantly lower values than the control and fentanyl group

Table 9 : Heart Rate, Systolic Blood Pressure, Diastolic blood pressure and Mean arterial Pressure at 5 minutes

At 5 minute	Control Group	Esmolol Group	Fentanyl Group	'p'	Significance
Heart Rate	93 ± 11.2	86 ± 8.4	91.7 ± 9.5	**0.034**	**Significant**
Systolic B.P	130.7 ± 7.9	121.3 ± 10.0	127.7 ± 6.7	**0.0016**	**Significant**
Diastolic B.P	81.8 ± 4.7	78.2 ± 5.4	81.6 ± 6.2	**0.0365**	**Significant**
Mean arterial pressure	98.2 ± 5.1	92.6 ± 6.3	97 ± 5.2	**0.0015**	**Significant**

Table shows the mean heart rate, mean systolic and diastolic blood pressure at 5 minutes following intubation.

There is statistically significant difference in mean heart rate of the three groups ($p < 0.001$).

The mean systolic diastolic blood pressure among patients in esmolol and fentanyl groups are significantly different from the control group.

Table 10

CHANGES IN HEART RATE AT VARIOUS TIME INTERVALS

Heart rate at	Control Group	Esmolol Group	Fentanyl Group
Basal	81.9 ± 12.9	86.9 + 10.8	87.4 + 11.9
At Study drug	89.2 ± 11.9	87.2 ± 10.5	90.8 ± 14
After induction	92.1 ± 11.4	81 ± 9.8	88.2 ± 11.6
At laryngoscopy and intubation	108.6 ± 11.6	91 ± 10.6	102.7 ± 11.9
1 Minute	110.6 ± 11.6	92.4 ± 10.8	103.5 ± 12.5
2 minutes	105.2 ± 11.4	90.3 ± 8.4	100.3 ± 10.3
3 minutes	100.9 ± 9.9	88.6 ± 9.2	96.8 ± 9.4
4 minutes	98.7 ± 10.3	86.5 ± 8.9	93.5 ± 8.9
5 minutes	93 ± 11.2	86 ± 8.4	91.7 ± 9.5
7 minutes	81.7 ± 12.9	86.9± 10.9	87.7± 11.3

Table 11

SYSTOLIC BLOOD PRESSURE AT VARIOUS TIME INTERVALS

Systolic blood pressure at	Control Group	Esmolol Group	Fentanyl Group
Basal	123.5 ± 7.9	127.8 ± 9.5	127 ± 8.4
At Study drug	124.2 ± 9.8	125.2 ± 11.4	126.2 ± 10.1
After induction	123.6 ± 8.9	117.1 ± 11.2	118.4 ± 10.9
At laryngoscopy and Intubation	152.1 ± 8.6	139.6 ± 7.2	142.8 ± 12.1
1 Minute	157.2 ± 6.9	139.2 ± 9.2	142.9 ± 12.1
2 minutes	150 ± 8.5	133.5 ± 7.5	139.5 ± 11.2
3 minutes	144.4 ± 9.6	128.4 ± 7.9	134.2 ± 9.1
4 minutes	137.8 ± 9	126.4 ± 8.3	129 ± 8.5
5 minutes	130.7 ± 7.9	121.3 ± 10	127.7 ± 6.7
7 minutes	125.1± 6	128 ± 8.2	126.8± 8.3

Table 12

DIASTOLIC BLOOD PRESSURE AT VARIOUS TIME INTERVALS

Diastolic B.P at	Control Group	Esmolol Group	Fentanyl Group
Basal	78.3 ± 5.7	81 ± 5.2	82.5 + 4.9
At Study drug	79.2 ± 5	80.2 ± 5.2	81.9 + 7
After induction	79.3 ± 5.7	76.6 ± 5.7	76.2 + 6
At laryngoscopy and Intubation	95.2 ± 6.5	88.6 ± 6	94.6 ± 11.1
1 Minute	99.1 ± 6	88.7 ± 5.9	94.6 ± 10.5
2 minutes	95.5 ± 6.6	84 ± 5.1	90.8 ± 11.2
3 minutes	91.6 ± 6.9	81.9 ± 5.8	88 ± 8.8
4 minutes	87.3 ± 6.7	80.4 ± 5.7	81.8 ± 6.7
5 minutes	81.8 ± 4.7	78.2 ± 5.4	81.6 ± 6.2
7 minutes	78.8± 4.4	79.6± 3.4	82.2± 4.5

Table 13

MEAN ARTERIAL PRESSURE AT VARIOUS TIME IN MINUTES

Mean arterial pressure at	Control Group	Esmolol Group	Fentanyl Group
Basal	93.6 ± 6.1	96.6 ± 6.2	97.3 ± 5.4
At Study drug	94.4 ± 6.1	95.2 ± 6.9	97 ± 6.9
After induction	94 ± 6.5	90 ± 6.9	90.4 ± 6.2
At laryngoscopy and Intubation	113.5 ± 6.5	105.7 ± 5.5	110.6 ± 10.7
1 Minute	118.6 ± 5.4	105.6 ± 5.9	110.6 ± 10.3
2 minutes	113.2 ± 6.3	100.5 ± 4.9	106.8 ± 10
3 minutes	109.6 ± 7.3	97.3 ± 5.7	102.8 ± 8.2
4 minutes	104.3 ± 7.1	95.8 ± 6.1	97.6 ± 4.6
5 minutes	98.2 ± 5.1	92.6 ± 6.3	97 ± 5.2
7 minutes	94± 5.4	96.8± 5.3	97.6± 4.1

The peak increase in heart rate, Systolic blood pressure, diastolic blood pressure noticed during laryngoscopy and endotracheal intubation in control group took 7 min to reach the preinduction value.

In fentanyl group, mean heart rate took about 7 min to reach the pre induction value, where as the mean systolic, diastolic blood pressure took about 4-5 minutes to reach the preinduction value.

In esmolol group. mean heart rate, mean systolic, diastolic blood pressure reached the pre induction values within 3 minutes.

DISCUSSION

Larngoscopy and endotracheal intubation frequently induce a cardiovascular stress response characterized by hypertension and tachycardia. This sympathoadrenal stress response to laryngoscopy results in an increase in myocardial O_2 demand leading to ischemia and acute heart failure in susceptible individuals.

In view of the frequent occurrence of hypertension and tachycardia during laryngoscopy even in normotensive individuals, it is perhaps rather surprising that complications have not been met very often. One reason for this may be the transient nature of hypertension which usually lasts less than 10 minutes. It is possible however that some of the complications that occur during intubation or even later in the course of anaesthesia may be precipitated by an episode of hypertension and tachycardia, following endotracheal intubation. ELLIOF (1980) observed left ventricular wall dysfunction following endotracheal intubation.

This reflex sympathetic response may be diminished or modified locally, centrally and peripherally and attempts have been made to accomplish this using all these approaches with varying success.

In an attempt to blunt these potentially adverse haemodynamic responses, different techniques and agents were used by many with varying success.

KING et al (1951) used ether, WYCOFF et al (1960) and J.KENNETH (1974) tried a combination of topical anaesthesia of larynx together with superior laryngeal nerve block to attenuate the stress response to endotracheal intubation.

STEINHAN and GASKIN (1963) used intravenous lignocaine, JAMES et al (1981) used lignocaine intratracheal spray, MASSON AND ECKANGOFF (1971) and DENLINGER J.K. (1974) and STOELTING (1978) used a combination of viscous lignocaine and topical intratracheal lignocaine and in 1979 LEAKO used a bolus of Sodium nitroprusside.

J.CURRAN et al (1980) tried droperidol, A.J.COLE and C.JORDAN (1980) and RICHARD et al (1981) studied the effect of β blockers using metaprolol and propranolol respectively. LUNN (1979) BENNET and STANLEY (1980) and DONAL E.MARTIN (1982) studied the effect of fentanyl in attenuating the intubation stress response.

Inhalation agents when used required deep levels and may delay recovery after short surgeries and can cause cardio vascular depression.

Adrenergic blockers are effective but may outlast the transient intubation response and may cause profound hypotension and bradycardia. Sudden withdrawal results in rebound hypertension.

Use of Vasodilators like Sodium nitroprusside results in reflex tachycardia, lability in blood pressure, cerebral vasodilation with elevation of intracranial pressure and pulmonary venous admixture.

Esmolol an ultra-short acting cardioselective β blocker does not have these short comings.

The factors favouring its value in obtunding the responses to laryngoscopy and endotracheal intubation include (M.VUCEVIC et al 1992).

1. It is a highly cardioselective agent analogous to metaprolol and so is unlikely to induce bronchospasm.
2. It has rapid distribution half-life of about 2 minutes and undergoes rapid esterase-mediated metabolism characterized by an elimination half-life of 9.2 minutes and rapid offset of action.
3. No significant drug interaction.

So this study was done to compare the effects of single bolus esmolol and fentanyl versus control group in attenuating the haemodynamic response to intubation.

Bolus injection of esmolol (2mg/kg) given 3 minutes prior to intubation provided consistent and reliable protection against increases in mean heart rate during laryngoscopy and endotracheal intubation and there after.

Bolus injection of fentanyl (3 mcg/kg) given 3 minutes prior to intubation failed to attenuate the heart rate to the same extent as esmolol during laryngoscopy and endotracheal intubation and thereafter. At each level the difference in mean heart rate between esmolol group & fentanyl group is statistically insignificant compared to control group.

Both esmolol and fentanyl are effective in protecting against increase in mean systolic blood pressure with no detectable difference between them at each level. This confers with the study of FENQ CK et al in 1996.

With esmolol, mean systolic and diastolic blood pressure returned to baseline value within 3minutes after intubation, whereas it was 5 minutes with fentanyl. This is in accordance with the study of M.HELFMMAN et al (1991).

Thus esmolol, a cardioselective β blocker would be useful to attenuate the sympathoadrenal response accompanying laryngoscopy and endotracheal intubation.

SUMMARY

This study is done to compare the efficacy of bolus injection of esmolol and fentanyl in attenuating the sympathoadrenal response accompanying laryngoscopy and endotracheal intubation in 75 patients divided into 3 groups.

Group C - Control

Group E - Esmolol

Group F - Fentanyl

In control group, the mean basal heart rate was 81.9 beats / minute and reached maximum of 110.6 beats/minute at 1 minute following laryngoscopy and endotracheal intubation and came back to the basal value of 81.7 beats/minute at 7 minutes.

In esmolol group, the mean basal heart rate was 86.9 beats / minute which reached maximum of 92.4 beats/minute at 1 minute following laryngoscopy and endotracheal intubation and came back to the basal value of 86.5 beats/minute at 4 minutes following laryngoscopy and intubation.

In fentanyl group, the mean basal heart rate was 87.4 beats / minute and reached maximum of 103.5 beats/minute at 1 minute following laryngoscopy and endotracheal intubation and came back to the basal value of 87.7 beats/minute at 7 minutes following laryngoscopy and intubation.

In control group, the mean basal systolic and diastolic blood pressure was 123.5mmHg and 78.3mmHg respectively and reached maximum of 157.2mmHg and

99.1mmHg respectively at 1 minute following laryngoscopy and endotracheal intubation and came back to the basal value at 7 minutes.

In esmolol group, the mean basal systolic and diastolic blood pressure was 127.8mmHg and 81mmHg respectively and reached maximum value at 1 minute following laryngoscopy and endotracheal intubation and came back to the basal value at 3 minutes following intubation.

In fentanyl group, the mean basal systolic and diastolic blood pressure was 127mmHg and 82.5mmHg respectively and reached maximum value at 1 minute following laryngoscopy and endotracheal intubation and came back to the basal value at 5 minutes following intubation.

It was observed that bolus injection of esmolol (2mg/kg) given 3 minutes prior to intubation provided consistent and reliable protection against increases in mean heart rate and mean systolic and diastolic blood pressure during laryngoscopy and endotracheal intubation and thereafter, compared to control group and fentanyl group.

Whereas Fentanyl (3mcg/kg) 3 minutes prior to intubation failed to attenuate the raise in mean heart rate to the same extent as esmolol, it attenuates the mean systolic, diastolic blood pressure to the same extent as compared to esmolol group.

With esmolol, the return of mean systolic, diastolic blood pressure to preoperative value was relatively earlier when compared to fentanyl.

In this study, Esmolol and fentanyl both atteneuated the rise in blood pressure though Esmolol was better. Esmolol attenuated the rise in heart rate with laryngoscopy and endotracheal intubation whereas fentanyl failed to protect against the rise in heart rate.

CONCLUSION

Bolus injection of fentanyl 3 mcg/kg 3 minutes prior to laryngoscopy and endotracheal intubation, attenuate the rise in blood pressure but failed to protect against the elevation of heart rate.

Bolus injection of esmolol 2 mg/kg 3 minutes prior to laryngoscopy and endotracheal intubation, attenuates both rise in heart rate and blood pressure and reaches the basal value earlier than the fentanyl group.

Thus Esmolol, a cardioselective β blocker produces brief and predictive control over the pressor response (heart rate and blood pressure) attenuation when compared to fentanyl which causes the control of blood pressure during laryngoscopy and endotracheal intubation.

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PROFORMA

COMPARATIVE EVALUATION OF BOLUS ADMINISTRATION OF ESMOLOL AND FENTANYL FOR PRESSOR RESPONSE ATTENUATION DURING LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

Name : Age : Sex : Date :

Theatre : Unit : IP No.: AssessNo.:

Address :

Diagnosis : Surgery :

Anaesthesia :

Pre anaesthetic Assessment :

Height	PR	CVS	Airway
Weight	BP	RS	ASA

Investigations :

Hb %

Urine Sugar

Albumin

Blood Sugar

Urea

Creatinine

Premedication :

Drug	Dose	Route	Time
1. Inj. Midazolam	0.05 mg / kg	IM	
2. Inj. Glycopyrrolate	0.02 mg / kg	IM	

Study Drug :

Group :

Parameters Time	PR per min	Systolic BP mm Hg	Diastolic BP mmHg	MAP mmHg
Basal				
At study drug				
After induction				
At laryngoscopy and intubation				
1 min				
2 min				
3 min				
4 min				
5 min				
7 min				

Intra operative complications :

Recovery room condition :

Post operative visit :

Characteristics of Beta Adrenergic Receptors

Receptor	Agonists	Tissue	Responses	Molecular mechanism
Beta 1	Iso > Epi = NE Dobutamine	a. Heart b.Juxta glomerular cells	Force and rate of contraction and AV nodal conduction velocity Renin secretion	Activation of adenylcyclase and Calcium channels
Beta 2	Iso > Epi = NE Terbutaline	a. smooth muscles (vascular, bronchial, GIT and genitourinary) b. Skeletal muscle c. Liver	Relaxation Glycogenolysis uptake of pottasium Glycogenolysis gluconeogenesis	Activation of adenyl cyclase
Beta 3	Iso=NE>EPi	Adipose tissue	Lipolysis	Activation of adenyl cyclase

Iso - Isoproterenol

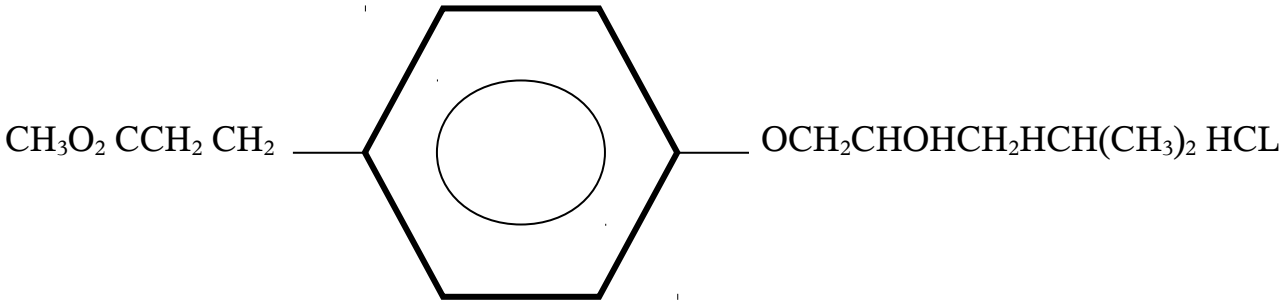
Epi - Epinephrine

NE - Norepinephrine

Site of β_1 Receptors and responses of Effector organs to autonomic nerve impulses

Effector organs	Receptor Type	Adrenergic responses	Cholinergic responses
A. HEART			
SA Node, Atria	β1	↑ H.R. ++ ↑ Contractility and Conduction velocity ++	↓H.R. Vagal arrest +++
AV Node	β1	↑ Automatically and conduction velocity ++	↓ Contractility and shortened AP duration ++
His-Purkinje system	β1	↑ Automatically and conduction velocity ++	↓ Conduction velocity AV block +++
Ventricle	β1	↑ Contractility, conduction velocity, automaticity and rate of idioventricular pace makers +++	Little effect
B. RENAL ARTERIOLES	β1 + β2	↑Constriction dilatation ++	
C. INTESTINE Motility and tone	β1 + β2	Decrease	Increase
D. KIDNEY Renin secretion	α 1 + β1	Decrease + Increase ++	

STRUCTURE OF ESMOLOL



STRUCTURE OF FENTANYL